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Meal Test for Glucose-Dependent Insulinotropic Peptide (GIP) in Obese and Type 2 Diabetic Patients

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Summary

Glucose-dependent insulinotropic peptide (GIP) contributes to incretin effect of insulin secretion which is impaired in Type 2 diabetes mellitus. The aim of this study was to introduce a simple meal test for evaluation of GIP secretion and action and to examine GIP changes in Type 2 diabetic patients. Seventeen Type 2 diabetic patients, 10 obese non-diabetic and 17 non-obese control persons have been examined before and after 30, 60 and 90 min stimulation by meal test. Serum concentrations of insulin, C-peptide and GIP were estimated during the test. Impaired GIP secretion was found in Type 2 diabetic patients as compared with obese non-diabetic and non-obese control persons. The AUC_{GIP} during 90 min of the meal stimulation was significantly lower in diabetic patients than in other two groups ($p<0.03$). Insulin concentration at 30 min was lower in diabetic than in non-diabetic persons and the GIP action was delayed. The ΔIRI/ΔGIP ratio increased during the test in diabetic patients, whereas it progressively decreased in obese and non-obese control persons. Simple meal test could demonstrate impaired GIP secretion and delayed insulin secretion in Type 2 diabetic patients as compared to obese non-diabetic and non-obese healthy control individuals.

Key words

Glucose-dependent insulinotropic peptide • Type 2 diabetes mellitus • Obese non-diabetic subjects • Insulin secretion

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Introduction

Postprandial glucose concentration is controlled by insulin secretion regulated both directly by the absorbed nutrients and through the secretion of incretin hormones, namely glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) (Meier and Nauck 2005, Yamada *et al.* 2006). The incretin effect contributes to the postprandial insulin release by about 40-70 % in healthy persons, whereas in type 2 diabetic patients this effect is markedly reduced (Holst 2008). The mechanisms underlying the loss of incretin effect have not been completely elucidated, although two defects have been suggested. First, a decreased GLP-1 availability in Type 2 diabetic patients has been described which may be caused either by defects in GLP-1 secretion or by increased inactivation through dipeptidyl peptidase IV (DPP IV) (Holst 2008, Nauck *et al.* 1986). This mechanism is supported by the clinical evidence that the administration of GLP-1 analogues as well as DPP IV inhibitors improves insulin secretion and contributes to better glucose control in Type 2 diabetic patients (Holst 2008). Second possible mechanism may arise from diminished insulinotropic action of GIP within the beta-cells. An impaired response to GIP in terms of insulin secretion in Type 2 diabetes was proposed by Nauck *et al.* (1993). The loss of GIP effect may be caused by defective expression of GIP receptors (Holst *et al.* 1997), downregulation of GIP signaling (Xu *et al.* 2007) or reduced beta-cell mass and function (Meier and Nauck 2004). GIP concentrations have been found to be normal, decreased or increased in Type 2 diabetic patients and

Table 1. Characteristics of Type 2 diabetic patients, obese non-diabetic patients and non-obese control persons.

	Control non-obese persons (n=17)	Obese non-diabetic persons (n=10)	Type 2 DM (n=17)
Age (years)	44 (31-58)	44 (21-62)	59 (43-71)
BMI (kg/m^2)	23.1 ± 3.1	38.0 ± 5.2^{b}	29.5 ± 4.5^{ax}
HOMA index	3.93 ± 1.52	6.81 ± 2.0^{b}	12.75 ± 8.37^{cy}
Cholesterol (mmol/l)	4.72 ± 1.54	4.77 ± 1.34	4.81 ± 0.83
HDL-cholesterol (mmol/l)	1.56 ± 0.4	1.41 ± 0.41	1.25 ± 0.35^{b}
LDL-cholesterol (mmol/l)	3.04 ± 0.67	2.98 ± 0.72	2.79 ± 0.70
Triglycerides (mmol/l)	1.00 ± 0.41	1.58 ± 0.93^{a}	1.95 ± 1.29^{c}

Results are expressed as mean ± SD or means with 2SD range. Statistical significance as compared to control group: ^{a} $p<0.01$, ^{b} $p<0.001$ and to obese non-diabetic persons: ^{x} $p<0.05$, ^{y} $p<0.01$

impaired GIP secretion is therefore unlikely (Knop *et al.* 2007a). In addition, it was not elucidated if diminished incretin effects could be a primary cause, potentially contributing to the development of Type 2 diabetes or if they would develop secondarily as a consequence of metabolic and hormonal disturbances in diabetes development. However, recent studies suggest that the incretin effects are diminished secondarily in the course of Type 2 diabetes (Knop *et al.* 2007b).

In addition to incretin effect, recent data indicate that GIP exerts the effects on adipose tissue and lipid metabolism to promote fat deposition and insulin resistance (Yamada *et al.* 2006). GIP receptors have been demonstrated on adipocytes and anabolic effects of GIP involving stimulation of glucose uptake, fatty acid synthesis and fatty acid incorporation into adipose tissue have been described (Yip *et al.* 1998). Fat ingestion increases GIP secretion from intestinal K-cells followed by their hyperplasia. Recent data confirm that GIP plays an important role in the pathogenesis of obesity and that GIP receptor blockade may protect from diet-induced obesity (Miyawaki *et al.* 2002).

The evaluation of GIP action may be clinically important. In the present study we developed simple mixed-meal test for screening of GIP changes in obese and Type 2 diabetic patients.

Patients and Methods

A total of 17 Type 2 diabetic patients, 10 obese non-diabetic persons and 17 non-obese healthy controls participated in this study. Subject characteristics are presented in Table 1. Normal glucose tolerance in obese non-diabetic persons was confirmed by oral glucose tolerance test. All persons had normal liver enzymes and serum creatinine concentration. Diabetic patients had proven diabetes for at least two years and were treated by metformin only. In a mixed meal challenge, breakfast composed from 200 ml Resource drink (Nestle, Prague) containing 28 g saccharides, 7 g fats and 18.8 g protein with one roll (50 g) and 10 g butter. The total caloric content of this standard testing breakfast was 445 kcal (1850 kJ). All examined persons gave their written consent and the study was approved by local Ethics Committee of the University Hospital.

Blood samples for biochemical analyses were drawn in the fasting state and then after 30, 60 and 90 min of the test. Glucose concentrations were measured in capillary blood samples using glucose oxidase method on glucose analyzer Super GLAmbulance (Dr. Müller Gerätebau, Freital, Germany), glycated hemoglobin HbA_1c by Imx GHb Assay System on Abbott Analyzer (Abbott, Chicago, USA) and expressed according to IFCC standards (normal values are 2.8-4.0 %). Serum total cholesterol, HDL- and LDL-cholesterol, triglycerides, urea, creatinine, uric acid and total protein concentrations were estimated in the central laboratory by routine methods on Hitachi analyzer. Serum insulin concentrations (IRI) were measured by radioimmuno-assay kits (CIS Bio International, Gif-Sur-Yvette Cedex, France) with normal values in the range of 9-24 mU/l in our laboratory. The cross-reactivity with proinsulin declared by the manufacturer was below 14 %. C-peptide concentrations were determined by radioimmunoassay kits (Immunotech, Czech Republic). Total GIP concentration was measured by radioimmunoassay kit (Phoenix Pharmaceuticals Inc., USA). AUC_{GIP} for 0-90 min was estimated in all patients. Differences in the

Table 2. Biochemical results from the standard meal stimulation.

	Control non-obese persons (n=17)	Obese non-diabetic persons (n=10)	Type 2 DM (n=17)
Glucose (mmol/l)			
0 min	5.1 ± 0.2	5.6 ± 0.2	8.9 ± 0.6^{cz}
30 min	6.5 ± 0.3	6.9 ± 0.2	11.3 ± 0.7^{cz}
60 min	5.7 ± 0.3	5.5 ± 0.2	13.2 ± 0.8^{cz}
90 min	5.6 ± 0.2	5.5 ± 0.2	13.0 ± 0.9^{cz}
Insulin (mU/l)			
0 min	17.3 ± 1.4	27.5 ± 2.7^{c}	30.7 ± 4.0^{c}
30 min	80.0 ± 13.4	151.9 ± 29.0^{a}	67.4 ± 10.0^{z}
60 min	58.6 ± 11.2	94.6 ± 10.4^{b}	87.8 ± 14.0^{a}
90 min	49.1 ± 9.0	71.4 ± 8.0^{a}	92.7 ± 14.0^{c}
IRI/Glucose			
0 min	3.45 ± 0.30	6.67 ± 1.50^{b}	3.48 ± 0.40^{y}
30 min	12.07 ± 1.76	23.7 ± 4.10^{b}	6.05 ± 1.20^{cz}
60 min	9.90 ± 1.36	22.2 ± 5.28^{b}	6.74 ± 1.10^{az}
90 min	8.60 ± 1.41	16.6 ± 3.90^{a}	7.67 ± 1.11^{z}
C-peptide (nmol/l)			
0 min	0.55 ± 0.05	1.37 ± 0.19^{c}	0.94 ± 0.09^{cx}
30 min	1.57 ± 0.11	2.83 ± 0.28^{c}	1.43 ± 0.13^{z}
60 min	1.36 ± 0.12	2.68 ± 0.13^{c}	1.80 ± 0.18^{az}
90 min	1.34 ± 0.11	2.48 ± 0.16^{c}	1.91 ± 0.19^{by}
GIP (pmol/l)			
0 min	49 ± 9	42 ± 5	44 ± 7
30 min	259 ± 49	251 ± 20	170 ± 15^{az}
60 min	207 ± 19	220 ± 26	180 ± 14^{ax}
90 min	195 ± 19	292 ± 30^{b}	163 ± 15^{az}
IRI/GIP			
0 min	0.54 ± 0.09	0.72 ± 0.08	0.83 ± 0.10^{b}
30 min	0.48 ± 0.10	0.63 ± 0.12	0.39 ± 0.05^{x}
60 min	0.30 ± 0.04	0.47 ± 0.08	0.50 ± 0.07^{b}
90 min	0.26 ± 0.04	0.27 ± 0.04	0.81 ± 0.28^{by}

The results are expressed as means ± SEM. Statistical significance compared to control non-obese persons: ^{a} $p<0.05$, ^{b} $p<0.01$, ^{c} $p<0.005$, and to obese non-diabetic subjects: ^{x} $p<0.05$, ^{y} $p<0.01$, ^{z} $p<0.005$

IRI (ΔIRI) and GIP (ΔGIP) concentrations at 30, 60 and 90 min related to basal values were used for comparison of dynamic hormone changes during the meal test. The ΔIRI/ΔGIP ratio expressing the insulin concentration change related to corresponding GIP change was calculated.

The insulin sensitivity in all individual persons was expressed by the Homeostasis Model Assessment (HOMA) index calculated from basal plasma glucose (G_0) and insulin (I_0) concentrations using the formula: (G_0 x I_0)/ 22.5 (Matthews *et al.* 1985).

The results were expressed as mean ± SEM. Repeated measures ANOVA model followed by Bonferroni multiple comparisons was used for evaluation of the relationships between hormone levels and factors. The ANOVA model consisted of between-subject factor status (diabetes, obese, controls), subject factor (extracting the inter-individual variability), within-subject factor time of the trial and status × time interaction. The original data was transformed by a power transformation prior ANOVA testing to attain Gaussian data distribution and homoscedasticity.

Pearson's correlation assessing the relationship between GIP or IRI/GIP index and diabetes duration, BMI, HbA1c or HOMA index was calculated.

Results

The results of biochemical variables in diabetic, obese and non-obese control subjects are shown in Table 2 and Figure 1. Diabetes control was assessed in diabetic patients by HbA1c which was significantly higher than in control non-obese persons (6.1±1.4 % vs. 3.6±0.4 %, $p<0.001$). Basal and postmeal hyperinsulinemia in obese non-diabetic subjects sustained normal glucose tolerance. This contrasted with delayed answer in the insulin secretion of Type 2 diabetic patients as compared to both obese and non-obese control persons (Fig. 1a). Similar picture of delayed insulin secretion in Type 2 diabetes was also obtained when insulin was related to glucose (Table 2). Serum insulin related to plasma glucose concentration in 30 and 60 min of the test was significantly lower in diabetic patients than in non-obese and obese non-diabetic subjects (Table 2). Basal GIP concentrations were comparable in all three groups. However, changes in GIP concentrations (ΔGIP) demonstrated diminished secretion in the first 30 min in Type 2 diabetic patients as compared with obese and non-obese control subjects (Fig. 1b) and area under the curve AUC_{GIP} in 0-90 min was significantly smaler in diabetic patients than in non-diabetic subjects (13.6±3.8 vs. 17.5±6.5, $p<0.03$). The dynamic changes in ΔIRI/ΔGIP ratio were different in diabetic than in non-obese or obese control persons (Fig. 1c). Progressive decrease of this ratio in obese and non-obese control persons contrasted with increasing ratio observed in Type 2 diabetic patients during the test.

Positive relationship was found between diabetes duration and both GIP concentrations at 60 and 90 min ($r = 0.47$ and $r = 0.49$, $p<0.05$) and GIP increments (ΔGIP) ($r = 0.41$ and $r = 0.42$, $p<0.05$) whereas no significant relationship was observed at basal state and at 30 min of the test. Diabetes duration was inversely related to IRI/GIP ratio at 60 and 90 min of the test ($r = –0.35$ and $r = –0.42$, $p<0.05$). No significant effect of insulin resistance expressed by HOMA index on GIP secretion was observed in any of the groups.

We could not prove any relationship between diabetes control assessed by HbA1c and GIP concentration or other variables.

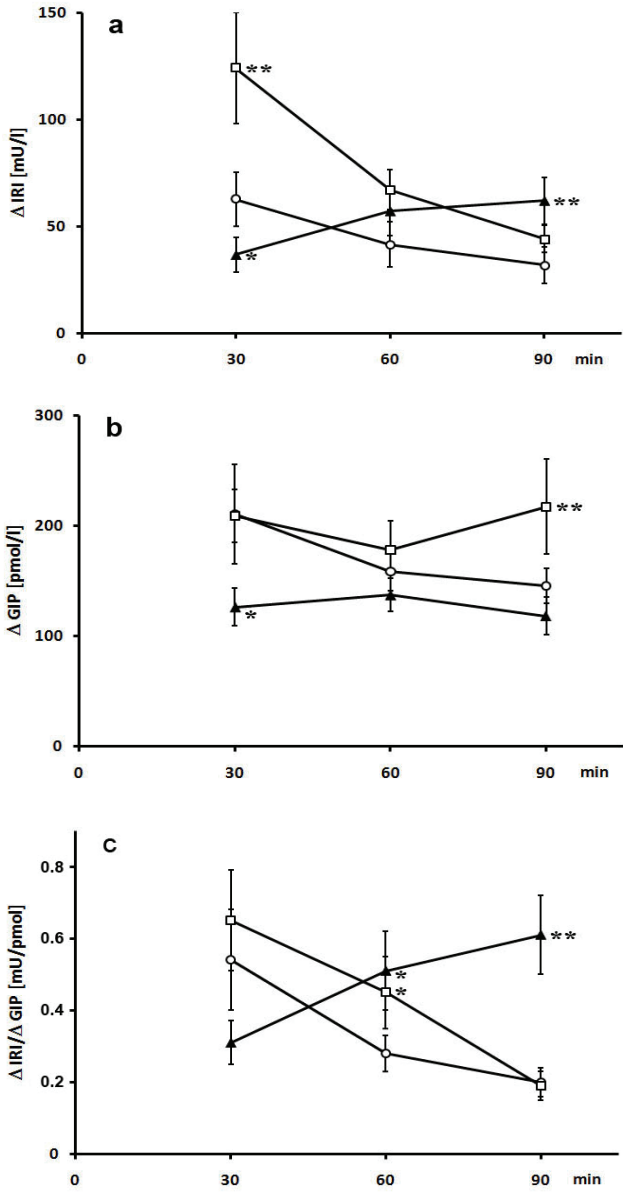

Fig. 1. Increment in serum insulin concentration (ΔIRI) **(a)**, plasma GIP concentration (ΔGIP) **(b)**, and ratios between increment of insulin and GIP concentrations (ΔIRI/ΔGIP) **(c)** related to basal values. Time course of variables in Type 2 diabetic patients (triangles) and obese persons (squares) are compared with controls persons (circles). Statistical significance compared to non-obese controls: $^{*}p<0.01$, $^{**}p<0.001$

Discussion

In the present study we developed simple meal test which may prove the changes in GIP secretion and action under different conditions. In comparison with usually used oral glucose tolerance test (oGTT) this meal test is more physiological as it contains all main nutrients.

We found no difference between basal plasma GIP concentration in diabetic and obese persons as

compared to control persons. The changes of serum GIP concentrations in diabetic patients were comparable with those in obese and non-obese control persons, although the GIP concentration at 30 min was significantly lower in patients with diabetes. This caused lower increment of GIP concentration supposing lower acute GIP secretion stimulated by the mixed meal in diabetic patients.

In addition, the GIP area under the curve (AUC_{GIP}) in diabetic patients was significantly smaller than in non-obese and obese non-diabetic persons. These results demonstrate that impaired GIP secretion may be present in Type 2 diabetic patients. This observation is in agreement with other reports (Toft-Nielsen *et al.* 2001), whereas significant increase of GIP stimulation in Type 2 diabetes was reported previously (Vollmer *et al.* 2008, Ross *et al.* 1977, Jones *et al.* 1989). We could not identify any factors influencing the lower GIP secretion in our diabetic patients.

Delayed insulin secretion was observed in Type 2 diabetics in comparison with non-diabetic control persons. We found that both IRI/GIP and ΔIRI/ΔGIP ratios during the test have similar changes in control non-obese and obese persons but they were different in Type 2 diabetic patients. The ΔIRI/ΔGIP ratio progressively decreased in subjects without diabetes, whereas it increased in diabetic patients during 90 min after meal stimulation. It may be interpreted that beta-cells in Type 2 diabetes are insensitive to meal and to the stimulation by incretin hormone GIP in the acute phase (in the first 30 min after meal stimulation). This is also supported by the strong association with delayed insulin secretion. Impaired GIP stimulation of the beta-cell, lacking GLP-1 effect and continual blood glucose increase may cause the observed abnormal course of IRI/GIP and ΔIRI/ΔGIP ratios during the test.

Reduced incretin effect in Type 2 diabetes with impaired insulin secretion was described earlier (Nauck *et al.* 1986, Nauck *et al.* 1993) and defective GIP receptor expression has been suggested (Holst *et al.* 1997, Xu *et al.* 2007). Down-regulation of pancreatic GIP receptors causing impaired beta-cell sensitivity to GIP was found in diabetic and obese rats compared to non-obese controls (Younan and Rashed 2007). The improved diabetes control in diabetic rats was associated with restored GIP sensitivity and chronic hyperglycemia was therefore regarded as a cause of down-regulated GIP receptors (Piteau *et al.* 2007). Similar improvement of insulin response to GLP-1 and GIP was found in Type 2 diabetic patients following four weeks of near normalization of blood glucose (Hojberg *et al.* 2009). In our study we could not find any relationship between diabetes control and plasma GIP concentrations as well as IRI/GIP or ΔIRI/ΔGIP ratios. The impaired GIP effect increases with deterioration of glucose tolerance as demonstrated in patients with secondary diabetes due to chronic pancreatitis (Knop *et al.* 2007b). It further stresses that the incretin defect is more probably secondary in the course of Type 2 diabetes (Knop *et al.* 2007a). The elimination rate of GIP is similar in diabetic and healthy subjects and differences in dipeptidylpeptidase IV activities do not seem to contribute to the defective GIP insulinotropic effect in Type 2 diabetes (Vilsboll *et al.* 2006).

We could not demonstrate any relationship between insulin resistance expressed by HOMA index and stimulated GIP concentrations. Our higher HOMA index in control persons was explained by higher values of normal serum insulin concentration in our laboratory. Changes in glucose concentration during the test meal were not associated with GIP concentrations in diabetic and non-diabetic persons. We observed that longer diabetes duration was associated with decreased insulin release.

This study has some limitations. Firstly, short test of 90 min duration was used for the examination. The extension to 120 and 180 min would offer better data on GIP or insulin changes. However, we did not follow longer test because a shorter period can be more reliable for clinical practice. Ninety minutes were sufficient to demonstrate a difference between diabetic and non-diabetic subjects including obese individuals. Secondly, we could not differentiate between GIP and GLP-1 effects on beta-cell insulin secretion because only GIP concentrations were measured, whereas GLP-1 was not assessed. We cannot therefore conclude which factors may participate in delayed insulin secretion in Type 2 diabetic patients, although it has been supposed that both incretin changes are rather a consequence of diabetes than a cause of the disease. Thirdly, small samples of examined persons have been used in the present pilot study and therefore statistical significance of observed differences may be lower. Finally, we used significantly more obese non-diabetic than diabetic persons. However, we could not demonstrate any difference between non-obese and obese persons with normal glucose tolerance in GIP secretion.

In conclusion, our results of simple mixed meal test with physiological GIP stimulation proved impaired GIP secretion and delayed insulin secretion in Type 2 diabetic patients. No such effects were found in obese

non-diabetic persons. Further studies elucidating the role of improved chronic diabetes control on reversibility of GIP secretion will be necessary.

Conflict of Interest

There is no conflict of interest.

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